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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,773	01/26/2004	Hrair Kirakossian	138.00US	2462

33603 7590 10/19/2005

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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/765,773	KIRAKOSSIAN ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry & Claim Status

The amendment filed on June 29, 2005 has been acknowledged and entered.

Claims 1-8 are pending.

The terminal disclaimer filed has been approved.

Withdrawn Rejection(s)

Double Patenting Rejection is withdrawn herein due to the filing of a Terminal Disclaimer.

Maintained Rejection(s)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear of where the "capture antigen" is located with regards to the rare cell, i.e. on the cell? See also claim 4 for the same problem.

Claim 4 is indefinite because the last step "identifying .....to determine the one or more biomarkers.." is inconsistent with the preamble of the claim "detecting one ore more protein-protein complexes..".

NEW GROUND(S) OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention: - the instant invention is directed to a method of detecting one or more biomarkers of a rare cell type in a sample containing a mixed population of cells, the method comprising the steps of immunomagnetically isolating from the sample a subpopulation of cells containing a rare cell type by contacting the sample with one or more antibody compositions, each composition is specific for a capture antigen and is attached to a magnetic particle; providing a binding compound with a releasable tag for one or more biomarkers on the cells, combining the subpopulation with the binding compound for each of the plurality of biomarkers such

that in the presence of the biomarker a complex is formed between each biomarkers and the binding compound specific thereof; releasing the molecular tags from the complex and separating and identifying the released molecular tags to determine the one or more biomarker in the sample.

The state of the art: - the prior art (US 6,815,212) Ness et al. teaches a method for detecting the binding of a first member to a second member of a ligand pair, comprising combining a set of first tagged members (binding compound with tag) with a biological sample (subpopulation of cells) which may contain one or more second member (cells) to permit the binding of the first and second members; ***separating the bound from the unbound*** and then releasing the tag from the first member and detecting the tag. (see abstract).

The predictability or lack thereof in the art:- in view of the lack of a separation step of the bound from unbound before cleaving the tags for analysis, the predictability is low.

The amount of direction or guidance present: - the instant specification fails to provide guidance on how meaningful results could be obtained without separating the unbound from the bound tags before cleaving the tags for detection.

The presence or absence of working examples:- there is no examples in the specification that shows that the detection is possible without separating the bound from the unbound before cleaving the tags for detection.

The quantity of experimentation necessary: - it would require an undue amount of experimentation for a skilled artisan to make and use the invention as claimed because

without a separation step of the bound tags from the unbound tags, all the tags (including the unbound) would be cleaved from the first member and no meaningful results could be obtained.

The relative skill of those in the art: The level of skill in the art is high.

The breadth of the claims:- the claimed method is directed to detection of a cleavable tags which bind to a binding compound specific for the biomarker of a target cell.

Since Ness requires that there must a separation step of the unbound and bound tags, and it is also well known in the art to separate the bound from the bound, without such separation, all the tags including the unbound tags, would be cleaved off from the first member and all the tags would be detected. Thus, detection of just the tag cleaved from the binding compound that was bound to the biomarker is impossible.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites in step 3 that " providing ....a binding compound for ***one or more biomarkers***" whereas in step 4 it recites "combining....a ***plurality of biomarkers***" which is inconsistent.

Claims 1 and 4 are also confusing because while there is only one cell type isolated, there are more than one biomarkers being detected. Usually if the cell type is a

cancer cell, then there is one cancerous biomarker on the cell. Thus, there would be only one kind of tag for such one type of cell or biomarker. However, claim 1 has a plurality of tags and then separating the released tags. If there is only one kind of tag being used for one kind of biomarker, then what other cleaved tags are there to be separated at the end before identifying the cleaved tag? The instant specification teaches on page 35 that "where a plurality of binding compounds are employed, separation of the tags is necessary". However, there is only one binding compound recited in claims 1 and 4. Thus, separation before analysis of the tags is unnecessary. Claim 1 is also indefinite for reciting "each binding compound /first binding compound having one or more molecular tags" and "each different binding compound /first binding compound ...". There is only "one" binding compound provided in the claim. It seems that there are more than one binding compound by such recitations- "each..".

Claim 4 is unclear of whether the first protein and second protein are the same as antibody composition and the capture antigen respectively.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Terstappen et al. (US 6,356,362) in view of Ness et al. (US 6,815,212).

Terstappen teaches a method of magnetically isolating a rare cell type from a mixed population of cells, the method comprises the steps of: mixing colloid magnetic particles conjugated with a monoclonal antibody reactive with the rare cell determinant or a class of determinants different than those found on blood cells with a population of cells containing a rare cell type; applying a magnetic field to isolated the bound complex from the unbound magnetic particles-antibody conjugates; Adding a second set of monoclonal antibodies (binding compound), labeled with reporter molecules (tag) to the isolated portion of the sample containing the rare cell type; separating the cells from the unbound by using a magnetic field; detecting the bound portion by microscopy, flow cytometry, or other analytical platforms such as bright field base image analysis, capillary volumetry, spectral imaging analysis, automated cell analysis. (see col. 8, lines 29-53). Detectable labels are detected based on light absorbance, fluorescence, reflectance, light scatter, phosphorescence, luminescence properties etc. (see col. 13, lines 45-50). Biospecific reagents are antibody having specificity for an epitope (biomarkers) which differs from that used to immunomagnetically select the cells. (see col. 16, lines 1-5). Terstappen also teaches detecting kinase receptor. (see col. 10, lines 45-50).

However, Terstappen fails to teach releasing the tags of the binding compound, separating and identifying the released tags to determine one or more biomarkers in the sample.

Ness teaches an assay method comprising of combining a set of first tagged members with a biological sample containing a second member of a ligand pair to

permit binding or formation of a complex between the first and second members; the second member may be attached to a solid phase such as magnetic particles (see col. 4, line 9); separating the bound first and second members from unbound members; cleaving the tag from the tagged first member and detecting the tag by spectroscopic such as mass spectrometers or potentiometric methods (see col. 14, line 65-col. 15, line 5). Mass spectrometers use the difference in the mass-to charge ratio of ionized atoms or molecules to separate them from each other. Mass spectrometry is therefore useful for quantitation of atoms or molecules and also for determining chemical and structural information about molecules. Molecules have distinctive fragmentation patterns that provide structural information to identify compounds. (see col. 62, lines 57-64). Detection is carried out using fluorescence tag and detecting their absorption, emission, etc. 9see col. 18,lines 43-65). A wide variety of first and second member pairs are used including nucleic acids, proteins, polypeptides (antibodies or antibody fragments – monoclonal or polyclonal or binding partners as a CDR- complementary determine region-), antibody/protein, antibody/antigen (see col. 40, lines 40-55). Samples are isolated and purified cell types (see col. 47, lines 24-25).

It would have been obvious to one of ordinary skills in the art to use cleave the tag and analyze the tags as taught by Ness as a detection step to detect biomarkers of cells isolated according to the method of Terstappen and would have a reasonable expectation of success because both references teach using magnetic particles as solid phase and detection based on light absorbance, fluorescence, reflectance, light scatter, etc. and both methods are applicable to cell samples. The advantage of cleaving a tag

after separation of bound and unbound is an enhanced sensitive detection method because the tag alone reduces non-specific background which might be produced if the target was bound to the tag.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Terstappen and Ness as applied to claim 1 above, and further in view of Wels et al. (US 5,571,894).

Terstappen and Ness have been discussed above.

However, both Terstappen and Ness fail to teach the capture antigen is a receptor tyrosine kinase.

Wels discusses that growth factors and their receptors are involved in the regulations of cell proliferation and they also play a role in tumor growth. Thus, c-erbB-2 growth factor receptor protein, a protein of the membrane receptor protein tyrosine kinase family is found in human breast tumors and human ovarian carcinomas. Thus, the c-erbB 2 protein has potential, both as a diagnostic marker and as a target for cancer therapy. (see col. 10-25).

Since Terstappen teaches using a kinase receptor as a receptor on cell for detecting cancer cells and Ness teaches a method of detecting cancerous cells, it would have been obvious to one of ordinary skills in the art to use antibodies that bind to erbB receptor of the tyrosine kinase receptor family as taught in Wels to detect cancer cells according to the combined method of Terstappen and Ness because cancer cells have erbB or tyrosine kinase receptor on their membrane.

Response to Arguments

Applicant's arguments filed June 29, 2005 have been fully considered but they are not persuasive.

Regarding the 112, 2nd paragraph rejection of claims 1 and 4, Applicants point out the definition of "capture antigen" in the specification. However, the spatial relationship of the "capture antigen" and the cells are not clear as recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding the 112, 2nd paragraph rejection of claim 4, the rejection is still maintained because the preamble and the last step of the method of claim 4 are inconsistent. Applicants fail to response to such rejection.

Allowable Subject Matter

Claims 4-8 are allowed.

The prior arts fail to teach a method of detecting a protein-protein complexes of a rare cell type in a sample containing a mixed population of cells such that each protein-protein complex has a first protein and a second protein, the method comprises the steps of immunomagnetically isolating from the sample a subpopulation of cells containing a rare cell type by contacting the sample with one or more antibody compositions, each antibody composition being specific for a capture antigen and being attached to a magnetic particle; providing a first binding compound conjugated with a cleavable tag; such first binding compound is specific for the first protein; and a second binding compound conjugated to a cleaving inducing moiety; such second compound is

specific for the second protein; combining the subpopulation, the first binding compound; the second binding compound so that the tag is cleaved; separating and identifying the released tags to determine the protein-protein complex in the sample.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
October 13, 2005

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10/14/05